PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004492	22.10.2004	24.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/00, A61K31/56, A61K31/57, A61K31/18, A61K31/569, A61M15/00, A61P11/00, A61P11/06

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/004492

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 18 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-19, 20 in part

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-10, 12-13, 17
	No:	Claims	1-5, 11, 14-16, 18-20
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	6-10, 12-13, 17
Industrial applicability (IA)	Yes:	Claims	1-17, 19-33
	No:	Claims	18

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/004492

III Non establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claim 18 as well as page 11, lines 6-9 of present description relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

IV Unity
Present application does not meet the requirements of Unity of Invention as defined in Rules 13.1, 13.2 PCT the reasons of which are specified in two different approaches (see subsequent sections 1 and 2) and which are to be seen complementary:

1) Special Technical Feature Approach
This International Preliminary Examination Authority found multiple groups of inventions in this international application, as follows:

1. Claims 1-19, 20 in part
Dry powder pharmaceutical compositions for inhalation therapy comprising calcium stearate and active agent

2. Claims 20 in part, 21-33
Inhalation device, medicament pack

D1 which is considered closest prior art discloses a dry powder for inhalation based on active particles comprising fluticasone or salbutamol and calcium stearate as additive material. Thus a physically and chemically stable composition, the delivery of accurate doses and a high fine particle fraction of active ingredients were achieved.

refer to invention no. 1:
There are thus no differences between the subject-matter of claims 1-5, 11, 14-16, 18, 19 and that disclosed in D1.
D1 does not disclose the form of calcium stearate, the weight percentage, the combination of the active ingredients (fluticasone propionate and salmeterol), the use of the active agents 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenylethyl}amino)hexyl]oxy}butyl)benzene-sulfonamide and/or 6alpha, 9alpha-Difluoro-17alpha-[(2-furanylcarbonyl)oxy]-11beta-hydroxy-16alpha-methyl-3-oxo-androsta-1,4-diene-17beta-carbothioic acid S-fluoromethyl ester.

The problem to be solved is a formulation for inhalation therapy, which has an increased fine particle dose, an improved stability performance and no detrimental effect on the fine particle dose caused by storage.

refer to invention no. 2:
details of the inhalation device and the medicament pack
The problem to be solved is the storage of the inhalation device and the successful storage as well as delivery of its content.

The features of the independent claims on file which make a contribution over the prior art, i.e. the special technical features, are as follows:
Claim 1: composition comprising calcium stearate, selection of further components and functional features
Claim 20: inhalation device

The special technical features are not identical. Neither the objective problems underlying the subjects of the claimed inventions, nor their solutions defined by the special technical features allow for a technical relationship to be established between the said inventions.
Consequently, the special technical features cannot be held to be corresponding.

2) Approach of Single Common Inventive Concept
The problem posed in the present application was a formulation for inhalation therapy, which has an increased fine particle dose, an improved stability performance and no detrimental effect on the fine particle dose caused by storage.

The solution, according to the Applicant, was a pharmaceutical dry powder composition for inhalation therapy which comprises calcium stearate and further active agents.

However, this is already reported by D1:
D1 which is regarded closest prior art discloses a dry powder for inhalation based on active particles comprising fluticasone or salbutamol and calcium stearate as additive material. Thus a physically and chemically stable composition, the delivery of accurate doses and a high fine particle fraction of active ingredients were achieved.

Therefore dry powder compositions comprising calcium stearate and an active agent for treating respiratory diseases is not only no longer novel, but also its combination with a medical device is already known.
It derives that the Common Inventive Concept or Technical Link, dry powder compositions for inhalation therapy comprising calcium stearate, is already known.

Furthermore, the Examination Division is unable to identify any Novel Common Inventive Concept (Common Technical Feature) linking the subsequent subject-matter:
composition for inhalation comprising calcium stearate and medical pack/inhalation device.

Therefore, it derives that the present application comprises several distinct subject-matters, namely:

composition for inhalation use
medical pack/inhalation device.

In the view of the different purposes of use for the above compositions/products, the Examination Division came to the conclusion that none of the compositions/products claimed can be laid together, so that the present application comprises the following two inventions 1) and 2):

1. Claims 1-19, 20 in part
Dry powder pharmaceutical compositions for inhalation therapy comprising calcium stearate and active agent

2. Claims 20 in part, 21-33
Medical pack/inhalation device

3) Final Remarks
The search has predominantly been carried out for the first invention characterised above.

In conclusion, therefore, the 2 groups of claims are not linked by common or corresponding special technical features and define 2 different inventions not linked by a single general inventive concept. The application - hence - does not meet the requirements of Unity of Invention as defined in Rules 13.1, 13.2 PCT. Accordingly, under the provisions of Rule 68.2 PCT, the applicant is invited to pay one additional examination fee.

In case the applicant prefers not to pay the additional fee and to restrict the application instead, one possible way for such a restriction could be the deletion of claims 21-33.

In the absence of any response from the applicant, the International Preliminary Examination Report will be established on basis of claims 1-19/20 in part, which claims appear to relate to the main invention.
The applicant is asked to state upon which invention further prosecution of the application should be based and to limit the application accordingly.

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Clarity
1.1) According to Article 6 and PCT International Preliminary Examination Guidelines Chapter III 5., 3.5, the claims shall be concise with reference to their entirety as well as to the individual claims. Further it should not be unduely burdensome to determine the matter for which protection is sought in terms of the presentation of claims and a multiplicity of alternatives in one claim.

With the present application, a redundancy of independent claims, unclear references of dependent claims to the contents of independent claims and a multiplicity of alternatives (such as ranges of technical features in one claim) cause a lack of clarity and cause doubts about the exact scope of the claims and the application. This particularly refers to the claims on the inhalation device, where the subsequent claims can be considered independent: 20, 22, 28, 29, 30, 31, 32, 33.

1.2) Claims 1-3 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved,
namely to increase fine particle dose (claim 1), to improve stability performance (claim 2), to eliminate or reduce the detrimental effect on fine particle dose caused on storage of said compositions (claim 3).
This merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

1.3) Claims 1-3 disclose the use of calcium stearate in dry powder pharmaceutical compositions for inhalation therapy to increase fine particle dose, improve stability, eliminate or reduce the detrimental effect on fine particle dose.
Claims 14-16 describe the methods of increasing fine particle dose performance, improving stability, eliminating/reducing the detrimental effect on fine particle dose.
The difference in terms of the content of said claims cannot be recognized so far. This causes a lack of clarity in the sense of Article 6 PCT.

2) Documents
The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US2003/0185764
D2: US2003/0162835
D3: US5641510
D4: WO03024396

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

3) Novelty - Article 33 (1) and (2) PCT

3.1) D1-D4 disclose dry powder formulations for inhalational delivery, whereas these compositions comprise calcium stearate besides other inactive ingredients and an active agent, which include fluticasone, salmeterol or ipratropium bromide. Fine and coarse excipient components are both lactose. Said compositions are used for the manufacture of a medicament for the treatment of respiratory diseases, also on the basis of the active principles and their well recognized indications in common practice.
Flowability, stability and fine particle fraction are increased (see e.g. D1).
In addition, an inhalational device is given for the right application of the dry powder formulations.

3.2) In the light of D1 -D4 (see sections V-2, 3.1) and under consideration of section III- 1., IV-1.-3., V-1.1-1.3, the subject-matter of claims 1-5, 11, 14-16, 18-20 is considered not novel according to Article 33 (1) and (2) PCT.

3.3) Consequently, - under consideration of III- 1., IV-1.-3., V-1.1-1.3. - the subject-matter of claims 6-10, 12-13, 17 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D4.

4) Inventive Step - Article 33 (1) and (3) PCT

4.1) The problem posed in the present application was a formulation for inhalation therapy, which has an increased fine particle dose, an improved stability performance and no detrimental effect on the fine particle dose caused by storage.

The solution, according to the Applicant, was a pharmaceutical dry powder composition for inhalation therapy which comprises calcium stearate and further active agents.

D1 which is regarded closest prior art discloses a dry powder for inhalation based on active particles comprising fluticasone or salbutamol and calcium stearate as additive material. Thus a physically and chemically stable composition, the delivery of accurate doses and a high fine particle fraction of active ingredients was achieved.

D1 does not disclose the form of calcium stearate, the weight percentage, the combination of the active ingredients (fluticasone propionate and salmeterol), the use of the active agents 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenylethyl]amino)hexyl]oxy}butyl)benzene-sulfonamide and/or 6alpha, 9alpha-Difluoro-17alpha-[(2-furanylcarbonyl)oxy]-11beta-hydroxy-16alpha-methyl-3-oxo-androsta-1,4-diene-17beta-carbothioic acid S-fluoromethyl ester and the details on the inhalation device/medical pack used for.

It appears to be obvious to a person skilled in the art to derive the use of said agents and combination of agents as well as a suitable device for the application of the dry powder suitable for inhalation therapy.

Unexpected or surprising effects do not seem to be connected with the use of said items.

4.2) Therefore, under provision of III-1., IV-1.-3., V-1.1-1.3., the subject-matter of claims 6-10, 12-13, 17 is obvious to a person skilled in the art due to general textbook knowledge and common experience. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

5) Industrial Applicability

For the assessment of the present claim 18 as well as page 11, lines 6-9 of present descrption on the

question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6) Further remarks

The Applicant's attention is drawn to the fact that the application must not be altered thus that its subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).